UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

MU

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/978,607	11/25/97	RAMIREZ	J 570068-9650

021675
BARRY EVANS
WHITMAN BREED ABBOTT AND MORGAN
200 PARK AVENUE
NEW YORK NY 10166

HM22/0315

EXAMINER	
SAIDHA, T	
ART UNIT	**PAPER NUMBER**
1652	11

DATE MAILED: 03/15/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)	
08/978007	Fastrez et al	
Examiner	Group Art Unit	
T. Sreedhar	1652	11

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 1/24/00.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 13-25 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 13-25 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

1. Applicants's amendment filed 1.24.2000 (Paper No. 10) along with new sequence listing is acknowledged. Claims 13-25 are pending.

2. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

3. Applicant's arguments filed as per the above cited amendment have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

4. New claim rejection:

Claims 13-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13 (lines 8-9) & 20 (lines 7-8) recite the phrases 'inserting a sequence.. or sequence of said starting enzyme..' and 'with a sequence of said mimetope..'. It is unclear what sequence(s) are being referred to as no SEQ ID NOs :, pertaining to the claimed recitation is identified or is apparent. Claim recitation identifying the SEQ ID Nos., or other suitable modifications will overcome this rejection.

Claims 14-19 & 21-25 are included in the rejection for failing to correct the defect present in the base claim(s).

Previous Rejections and Arguments :

35 U.S.C. § 112, first paragraph

5. Claims 13-25 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a method of determining the amount of an analyte in a test sample using a

chimeric β-lactamase as the starting enzyme, and comprising selected amino acids sequence insert in the loop of the rim of the active site residues 103-105, for example; or the alpha. 11 helix residues 271-272 of the R-Tem β-lactamase, for example; in order that the enzyme be defined as a chimeric enzyme, which are then selected for binding by antibodies psa10 and psa66. The claims are directed to a method of determining the presence of an analyte using any (a) chimeric enzyme as the starting enzyme, wherein said chimeric enzyme is constructed by inserting a sequence of said mimetope (binding site moiety) into a sequence of said starting enzyme or replacing at least one amino acid of the starting enzyme with a sequence of said mimetope. However, the guidance provided for a single site specific chimeric β-lactamase is inadequate for one skilled in the art to develop a method using any chimeric enzyme construct for determining the presence or amount of an analyte in a test sample.

Factors to be considered in determining whether undue experimentation is required, are summarized in *re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) | *Ex parte* Forman [230 USPQ 546 (Bd. Pat. App. & Int. 1986)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim. The factors most relevant to this rejection are the scope of the claims, unpredictability in the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

The claims are directed to a method for determining the presence of an analyte in a test sample using any enzyme as the starting enzyme, modifying the enzyme(s) to create a functional or

enzymatically active chimeric enzyme having a binding site moiety, to which a binding molecule can attach. From the guidelines provided for construction of chimeric β-lactamase and the skill of the artisan in the area of molecular biological and enzymology it would have been possible to make a number of single, double or multiple amino acid(s) modifications in the chimeric β-lactamase structure in order to selectively modify the catalytic sites, to enable modulation upon binding. Selective insertion sites have been identified, for example, the loop preceding the alpha -11 helix (residues 271-272 of β-lactamase. However, the transfer of such a construct to any amino acid modification within the β-lactamase enzyme or any other enzyme in order to first produce a chimeric enzyme and further attempt to selectively insert or replace single, double or multiple amino acid inserts and develop chimeric enzyme binding site moiety which can successfully attach itself to a binding molecules, lacks adequate guidance, is unpredictable and would result in undue experimentation. It lacks adequate guidance because the chimeric insertion developed for β-lactamase or the specific amino acid modifications made in order to develop the binding molecule to achieve the desired attachment to the molecule, is not a matter of routine. This is because the modification of amino acid(s) in the β-lactamase amino acid chain as achieved in the instant example, may not necessarily result in producing an active chimeric enzyme in every other enzyme because every other enzyme is distinct in its sequence, regions of active site or susceptibility to modifications, leading to highly unpredictable results. Thus, the specification fails to provide guidance to other enzymes, other than β-lactamase and at the specific positions, that can be successfully utilized in effectively creating chimeric enzymes and the appropriate steps required for such constructs. Every enzyme being distinct , it remains

unpredictable that the instant disclosure on β-lactamase be sufficient to develop a method for determining analytes using other any chimeric enzyme or any sequence insert (Clam 13) , which can successfully attach itself to any binding molecules (claims 14-19), or where the analyte and substrate contact the enzyme simultaneously or in steps (claims 20-25), or where the test sample contains the analyte (claim 25). Therefore, the skilled artisan would require guidance, such as the (a) the sequence of the β-lactamase (SEQ ID NO:) or the other chimeric enzymes (by SEQ ID Nos:) and guidance to where the sequence inserts of the mimetope (BSM), identification of the active catalytic and binding sites and the effect(s) of such modifications on the functionality of the different enzymes constructs, in order to make and use chimeric enzymes in a manner commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

6. Applicants Arguments:

It must be emphasized that the above rejection is under 35 U.S.C. § 112, first paragraph (enablement) and is not a written description rejection.

Applicants have failed to address the key issues of the rejection. On page 19, for example, the Applicants incorporate a portion of a paragraph from the previous Office Action, which is out of context. It is unclear what evidence the Applicants are looking for from the examiner. Please point to the lines of the Office Action the Applicants are referring to, as it not clear what the basis of Applicants' following conclusion is :

"However, the Examiner appears to be assuming his own conclusion: he has presumed that there is substantial variation in the sequence among various species of β-lactamase.....The Examiner has not provided any evidence to support this conclusion".

Sequence homology or conservation of sequence homology is relied upon in order to evaluate how certain amino acid changes would effect or alter the enzyme activity. In the instant case, for example, if an amino acid change is made in the structure of a specific β-lactamase at a specific position to obtain a chimeric β-lactamase, the same change and effect may be difficult to reproduce in another species of β-lactamase with a different structure, and even more difficult to obtain in another enzyme or protein or starting molecules, such as plasmin, prostate specific antigen, subtilisin, alkaline phosphatase, etc., having an entirely different structure or sequence. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, catalysis and in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions. However, applicants have provided little or no guidance beyond the mere presentation of specific sequence inserts in β-lactamase to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in any enzyme (or protein) which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and

the nature and extent of changes that can be made in these positions. Such a definition might also read on previously characterized proteins, or alternatively, might include proteins with additional functions or activities neither envisioned nor enabled by applicants in the current invention. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988) with regard to the issue raised above.

Applicants further argue that the Examiner maintains, without any evidence to support his conclusion, that β-lactamase includes a diverse number of enzymes, presumably having dissimilar sequence homologies and functionalities.

In response, Applicants submission of the MINIREVIEW (Bush et al. Antimicrobial Agents and Chemotherapy, 1995, 1211-1233), describes and supports the Examiner's point of view that there are diverse classes (A-D) of β-lactamases including Cephalosporins, Penicillin & β-lactams with differing sequence similarities. Figure 1, shows a dendrogram, describing the various β-lactamase and their structural relationships. Vertical branch lengths extending to the left are inversely proportional to the similarity between sequences.

Therefore a modification made in one type of the β-lactamase having a specific sequence may not necessarily translate to or appropriate to make in another kind of β-lactamase.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 13-14, 16-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Rodrigues et al. [Cancer Research 55 : 63-70, 1995]. Rodrigues et al. teach a method for the recombinant construction of Fv (dsFv) β-lactamase fusion (or chimeric or variant) protein for use in antibody-dependent enzyme mediated prodrug therapy. A control fusion protein Fv (dsFv) β-lactamase fusion (or chimeric) was constructed by installing the V11 mutation W95A and Y100aA into the dsFv3- β-lactamase using the oligonucleotide MLR125 5'-GCC....gca...TAC-3' (see page 65, column 1, line 28-36). This unique site was inserted or installed into the β-lactamase gene, so that the expressed protein will have a mimetope or binding site moiety in the amino acid sequence of the lactamase or starting enzyme facilitating the binding of antibody raised against the chimeric enzyme. The variant or chimeric enzyme is modulated upon binding the target antigen (see abstract & page 63 column 2 & page 64, Fig 2). Applicants definition of mimetope (page 2, lines 17-22) is the preferred BSM (binding site moiety) (claim 13, step 2) and a BSM is engineered into the target molecule by site directed mutagenesis (Page 64, Fig. 2; Page 65, column 1, lines 28-52) and the fusion protein then attaches to the antibody (or binding molecule). The specification defines 'analyte' as an antibody (page 21, lines 1-2). The fusion protein retains both antigen-binding plus kinetic activity (claim 13, step 3) (see abstract) in murine serum (test sample of claim 1, step 1). Kinetic parameters for purified β-lactamase and Fv (dsFv) β-lactamase fusion (or chimeric) (see Table 1) with the substrates cephalothin and PRODOX were determined by a described method. The reference identifies all the steps outlined in claim 13 or 20, as explained above. The claims are anticipated by the reference.

Applicants Arguments:

Applicants argue that not all the claim limitations are taught by the reference. Rodriques relates to the attachment of a portion of an antibody to β-lactamase as a targeting agent for use in prodrug therapy. Rather than inserting a mimetope sequence into the sequence of the starting enzyme or replacing a segment of the starting enzyme sequence with the mimetope, which mimetope is recognized by a binding molecules, Rodriques attaches an antibody, i.e., a binding molecules, directly to the starting enzyme to produce a fusion protein. The instant claims specifically require insertion of a mimetope into a starting enzyme, which is recognized and binds to a binding molecule. The attachment of the binding molecule to the chimeric enzyme modulates the activity of the chimeric enzyme. In contrast, Rodriques attaches the binding molecules (an antibody) directly to the starting enzyme and there is no modulation of the chimeric enzyme's activity as a result of the interaction between the chimeric enzyme and a separate binding molecule, which is not incorporated into the sequence of the chimeric enzyme.

In response it is pointed out that the binding molecule(s) is recombinantly inserted into the sequence (see page 65, column 1, lines 28-52) of the chimeric enzyme (also see Fig. 2) and is therefore modulated, and taught by Rodriques. All the elements being taught, the reference anticipates the claims.

In discussing the highlighted elements of the claims 13 & 20, Applicants refer to :

(1) A chimeric enzyme which has the same enzymatic activity as that of the starting enzyme.

Response : Such an activity is described for the purified β-lactamase & the dsFv3- β-lactamase (Page 65, see kinetic procedure, for example).

(2) A starting enzyme comprises a polypeptide.

Response : All enzymes are polypeptides.

(3) A mimetope inserted into the sequence of a starting enzyme or which replaces at least one amino acid in the sequence of the staring enzyme.

Response : As indicated above, binding molecule(s) is recombinantly inserted into the sequence (see page 65, column 1, lines 28-52) of the chimeric enzyme. Even it is attached as pointed out by the applicants, which is not the case, clearly the phrase "...or which replaces at least one amino acid in the sequence of the starting enzyme". Such a replacement could be any where in the sequence and such a replacement is also taught by the reference, for example, mutation W95A.

(4) The activity of the chimeric enzyme is modulated upon binding molecule to the mimetope.

Response : As indicated above binding molecule(s) is recombinantly inserted into the sequence (see page 65, column 1, lines 28-52) of the chimeric enzyme (also see Fig. 2) and is therefore modulated, and taught by Rodriques.

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the

THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15am to 4:45pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Tekchand Saidha
Art Unit 1652
March 9, 2000

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600